A REGIOSELECTIVE LITHIATION OF 1-METHOXYMETHOXYINDOLE AT THE 2-POSITION AND ITS APPLICATION FOR THE SYNTHESIS OF 2-SUBSTITUTED INDOLES[1]

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Abstract—— A regioselective lithiation of 1-methoxymethoxyindole at the 2-position was achieved with *n*-BuLi at 0°C. Subsequent treatment with electrophiles afforded 2-substituted 1-methoxymethoxyindoles, which were readily converted to 2-substituted indoles.

Much efforts have been focused on developing a new directing group for the regioselective lithiation at the 2-position[2] in the indole chemistry. The ideal directing group should realize the formation of 2-lithioindole species by the reaction with milder and safer lithium reagent, and the reaction temperature to be as close to room temperature as possible. Therefore, *n*-butyllithium (*n*-BuLi) is more favorable than *sec*-BuLi and *tert*-BuLi. In addition, the directing group must be removed under mild reaction conditions if necessary. Actually, almost all directing groups thus far known[2] require low reaction temperature (-76°C) and an extremely pyrophoric *tert*-butyllithium for the formation of 2-lithioindoles due to their instability at higher temperatures. An exception is a dimethylaminomethyl group which enables lithiation with *n*-BuLi under ice-sodium chloride cooling, but its removal was reported to be troublesome.[2c]

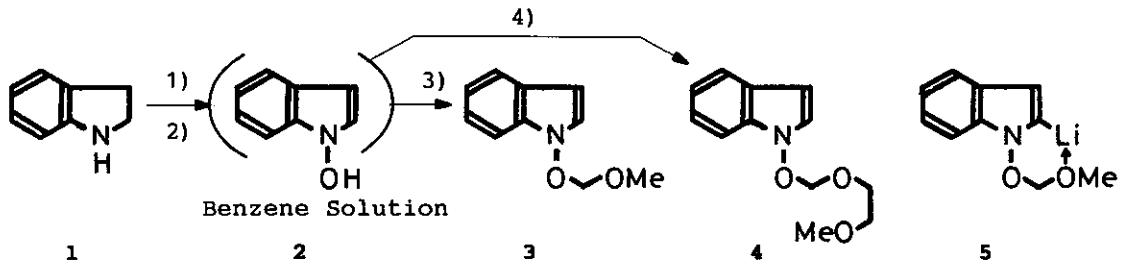
In the previous paper,[3] we reported that 1-methoxy group[4] was a suitable

directing group and regioselective lithiation at the 2-position was performed with *n*-BuLi at about -18°C (ice-sodium chloride). Nevertheless, when the reaction was carried out at 0°C, the yields of products dropped down to 30~50%. Now, we wish to report that 1-methoxymethoxy group is superior to the 1-methoxy group. Thus, 1-methoxymethoxyindole (**3**, Scheme 1) was regioselectively lithiated at the 2-position with *n*-BuLi at 0°C (ice cooling), and subsequent reaction with electrophiles produced the corresponding 2-substituted 1-methoxymethoxyindoles in good to excellent yields. The compound (**3**) was easily prepared as follows, though the optimum reaction conditions were not made. 2,3-Dihydroindole (**1**) was oxidized with sodium tungstate dihydrate[4] (0.2 mol eq.) and 30% aq. hydrogen peroxide (H_2O_2, 10 mol eq.) in methanol-water (10:1) for 15 min at room temperature, then the whole was extracted with benzene. After the extract was washed with water and dried over sodium sulfate, the resultant benzene solution containing 1-hydroxyindole (**2**) was treated with methoxymethyl chloride (3 mol eq.) in the presence of potassium carbonate (18 mol eq.) and tetra-*n*-butylammonium bromide (0.1 mol eq.) at room temperature, resulting in the formation of **3** (mp 27.0-27.5°C) in 31% yield. In the above procedure, urea hydrogen peroxide addition compound could also be used as an oxidizing reagent instead of 30% H_2O_2 with more effectiveness (yield of **3**, 39%). Similar trapping of **2** with 2-methoxyethoxymethyl chloride afforded 1-(2-methoxyethoxymethoxy)indole (**4**, oil) in 11% yield.

Treatment of **3** in anhydrous tetrahydrofuran with *n*-BuLi (1.1 mol eq.) at 0°C (ice bath) for 15 min under argon atmosphere produced yellowish brown solution (color of 2-lithium salt **5**), and subsequent addition of *N,N*-dimethylformamide at 0°C afforded 1-methoxymethoxyindole-2-carboxaldehyde (**6a**) in 96% yield. The reaction of **5** with other electrophiles also proceeded successfully and the results are summarized in Table I.

Catalytic hydrogenation of **6a-e** over 10% palladium on charcoal in methanol at room temperature and atmospheric pressure afforded the corresponding 2-

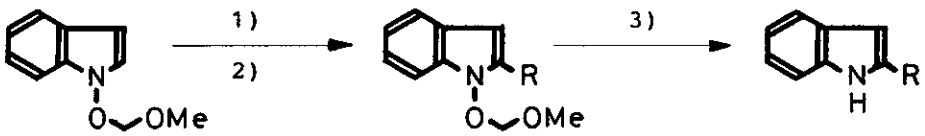
Scheme 1



1 2 3 4 5

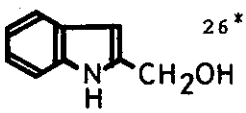
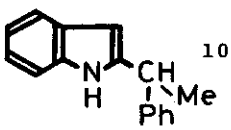
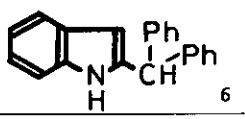
1) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2 or urea$\cdot H_2O_2$, MeOH-H_2O; 2) Benzene extraction; 3) MOM-chloride, K_2CO_3; 4) MEM-chloride, K_2CO_3.

Table I. Regioselective lithiation of 1-methoxymethoxyindole at the 2-position at 0°C and the syntheses of 2-substituted indoles



3 6 7

1) *n*-BuLi, THF, 0°C, 15 min; 2) Electrophiles; 3) 10% Pd/C, H_2, 15~60 min

Entry	Electrophile	R	Yield (%) of 6	Yield (%) of 7 + Other Product 8
1	Me_2NCHO	a) -CHO	96	67*2  26*2
2	$Me_2C=O$	b) $-C(OH)Me_2$	89*1	87 —
3	MePhC=O	c) -C(OH)MePh	88*1	76  10
4	Me_3SiCl	d) $-SiMe_3$	91	86 —
5	$Ph_2C=O$	e) $-C(OH)Ph_2$	99	90  6

*1 Starting material was recovered in 10% yields, respectively.

*2 The hydrogenation was carried out for 5 min at room temperature.

substituted indoles (**7a-e**) in good to excellent yields, as shown in Table I. In the case of entry 1, **7a** was produced in 67% yield together with 26% yield of 2-indolemethanol (**8a**) after hydrogenation for 5 min. The yield of **8a** was improved to 96% when the hydrogenation was carried out more than 10 min. In entries 3 and 5, benzylic hydroxy group was partly removed to produce **8c** and **8e** in 10 and 6% yields, respectively.

In summary, we could develop a simple 2-lithiation method of indoles. Utilizing **4** and other 1-hydroxyindole derivatives, attempts to realize 2-metalation at room temperature and biological evaluations are currently in progress.

REFERENCES AND NOTES

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Received, 10th April, 1992